UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,496	07/31/2001	Dmitry Vladimirovich Zybin	U 013571-6	4792

140 7590 09/10/2004

LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,496	ZYBIN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-38 and 42-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *31,32,34-38,44 and 45* is/are allowed.

6)☒ Claim(s) *24,25,30 and 33* is/are rejected.

7)☒ Claim(s) *26-29,42 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 39-41 have been canceled. Claims 24, 26, 28, 30, 31, 33, 36, and 38 have been amended. Claims 42-45 have been added. Claims 24-38 and 42-45 are pending and under consideration.

2. Sections of text from Title 35, U.S. Code, not found in this action can be found in a prior action.

3. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claim 33 is drawn t the method of claim 31 further comprising preparing a vaccine for said cultivated cells. The specification teaches that transplanted tumor cells within the polyacrylamide gel capsules grown in vivo can provide immune stimulation against shed tumor antigens which are small enough to penetrate the connective tissue capsule which forms around the injected polyacrylamide gel. The specification does not provide guidance for how to make a vaccine preparation based on said cultivated tumor cells. The term vaccine is defined by the art (Stedman's Medical Dictionary, 27th Edition, 2000, definition for "vaccine") as a prophylactic immunotherapeutic composition. Thus, the claimed vaccine would have to be able to prevent the growth of tumors in a patient and the specification provides no guidance as to selecting patients at risk for developing a specific type of tumor, and the time at which to begin administering said vaccine..

In the event that applicant amends the claims to "pharmaceutical composition" rather than "vaccine" the specification is still not enabling for how to make such a composition with respect to tumor cells. Immunotherapy of cancer by the administration of vaccines is highly unreliable. The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response,

failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). The specification has provided evidence that two T-cell clones are able to lyse tumor cells expressing an epitope of the claimed tumor rejection antigen precursors in vitro. Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion".. In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration,

whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. These references serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstract of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105) and the abstract of Algarra et al International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed vaccine upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teach that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules (abstract).

Paul (ibid) states that the induction of tolerance is a mechanism by which tumor cells escape immune detection. The art recognizes that T-cell are subject to clonal deletion within the thymus of a host and that this mechanism eliminates t-cell which are reactive with self-antigens. The specification teaches that the polypeptide encoded by SEQ ID NO:2 is indeed a self antigen, rather than a mutated self antigen, as it is expressed on normal tissues as well as cancerous tissues. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that clonal deletions of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor

cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete of shed antigens. In the instant case, the antigens are known self antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even thought P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. With regard to the isolation of two T-cells which are specific for the instant antigen presented in the context of HLA-A24, it cannot be determined if this is a reliable indicator that in all patients, with any of the types of cancers listed on page 20, would have a T-cell available after thymic selection which would react with said antigen in the context of HLA-A24 or any other MHC molecule. Further, the presence of CTL which can lyse target cells in vitro has no apparent nexus with anti-tumor cytolytic activity in vivo. Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-

725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the lysis of target cells expressing tumor antigens in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo.

Thus, it appears that the interaction of the tumor cells with the host can produce tolerance by means of clonal deletion within the thymus of said host. Furthermore, the relationships between the multitude of different tumor cells would be variable as different types of organs (neuroblastoma, brain, colorectal, gastric, head-and neck, lung, prostate, breast, thyroid, bladder, kidney, leukemia, etc) and different histological types of neoplasms (carcinoma, squamous cell, mesothelial, neuroepithelial, sarcoma, leukemia, etc) all present tumor antigens antigens.

It is concluded based on the references discussed above, that the state of the art with respect to treating patients with cancer by means of administering a vaccine made form tumor antigens is unpredictable. The specification does not provide any specific guidance on how to make such a vaccine. The specification does not provide any disclosure that the administration of tumor antigens taken from cells propagated by the claimed method would generate CTLs which lyse the cells of a tumor in situ,. Thus, without a demonstration that the administration of the a vaccine derived from the cells propagated by the claimed method which would overcome immunosuppression of the host, the rapid growth of the target tumor cells, as well as overcoming the stromal barrier and tolerance induction in the host and objective evidence that the target tumor cells in vivo present adequate tumor rejection antigen on the surface of all the tumor cells, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the vaccine produced from cells propagated by the claimed method.

4. Claims 24, 25 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Pavlyk et al (EP 742,022, cited in the previous Office action). Claim 24 is drawn to a method of forming in a mammal a connective tissue capsule for maintaining transplanted allogenic or xenogenic cells, comprising introducing a polyacrylamide gel into a tissue of the mammal so as to cause the connective tissue capsule to form around the polyacrylamide gel. Claim 30

embodies the method of claim 24 wherein the connective tissue capsule is formed by sub-Q injection of the polyacrylamide gel into the mammal.

Pavlyk et al disclose a method of making a connective tissue capsule in a mammal comprising the sub-Q injection of polyacrylamide hydrogel (page 10, line 56 to page 11, line 52). It is noted that the intended use of the capsule "for maintaining transplanted allogenic or xenogenic cells" does not influence the physical characteristics of the capsule. Thus, claim 24 encompasses methods of forming connective tissue capsules in a mammal comprising introducing a polyacrylamide gel into said mammal.

5. Claims 26-29, 42 and 43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

6. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants declarations and arguments..

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
9/7/2004

KAREN A. CANELLA PH.D.
PRIMARY EXAMINER